REVIEW

The neurocircuitry of addiction: an overview

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Drug addiction presents as a chronic relapsing disorder characterized by persistent drug-seeking and drug-taking behaviours. Given the significant detrimental effects of this disease both socially and economically, a considerable amount of research has been dedicated to understanding a number of issues in addiction, including behavioural and neuropharmacological factors that contribute to the development, loss of control and persistence of compulsive addictive behaviours. In this review, we will give a broad overview of various theories of addiction, animal models of addiction and relapse, drugs of abuse, and the neurobiology of drug dependence and relapse. Although drugs of abuse possess diverse neuropharmacological profiles, activation of the mesocorticolimbic system, particularly the ventral tegmental area, nucleus accumbens, amygdala and prefrontal cortex via dopaminergic and glutamatergic pathways, constitutes a common pathway by which various drugs of abuse mediate their acute reinforcing effects. However, long-term neuroadaptations in this circuitry likely underlie the transition to drug dependence and cycles of relapse. As further elucidated in more comprehensive reviews of various subtopics on addiction in later sections of this special issue, it is anticipated that continued basic neuroscience research will aid in the development of effective therapeutic interventions for the long-term treatment of drug-dependent individuals.

Keywords: abuse; addiction; animal models; dopamine; glutamate; mesocorticolimbic; neurobiology; relapse

Abbreviations: AMPA, N-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CPP, conditioned place preference; CRF, corticotropin-releasing factor; DA, dopamine; dmPFC, dorsomedial prefrontal cortex; ICSS, intracranial self-stimulation; NAcc, nucleus accumbens; NE, norepinephrine; OFC, orbitofrontal cortex; PFC, prefrontal cortex; VTA, ventral tegmental area

Introduction

Drug addiction is a chronic relapsing disorder characterized by compulsive drug-seeking and drug-taking behaviours, despite negative consequences. The American Psychiatric Association (1994) describes substance dependence as a set of symptoms mainly involving the inability to reduce or control drug use, with the recent National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration (SAMHSA, 2007) estimating that 22.6 million Americans 12 years of age or older, or 9.2% of the population, can be considered to have a substance abuse or dependence disorder (including alcohol or illicit drugs). Although evidence shows periodic declines in some areas of abuse patterns, the overall prevalence of substance abuse disorders remains unacceptably high. Moreover, one of the most significant problems for the long-term treatment of drug dependence is the high incidence of relapse to drug-seeking and drug-taking behaviours following months or years of abstinence (Dackis and O’Brien, 2001; Wagner and Anthony, 2002). Given the detrimental social and economic effects of drug addiction, a significant amount of research has been dedicated to ascertaining the neuropharmacological mechanisms mediating the development and persistence of substance abuse disorders. In this section of this special journal issue, we will provide a broad overview of how animal models of addiction and relapse have advanced our understanding of the neurobiology underlying drug-taking and drug-seeking behaviours. More detailed reviews regarding the role of genetics/proteomics (Harris and Mayfield) and neuroplasticity (Thomas, Kalivas and Shaham) in addiction, as well as discussions regarding specific drugs of abuse, including alcohol (Vengeliene, Molander and Spanagel), opiates (Christie), psychostimulants (McGregor), cannabis (Piomelli and Goldberg) and inhalants (Lubman, Yücel and Lawrence), and clinical interface into treatment (Nutt), will be provided in later sections.

Theories of addiction

Early theories of addiction postulated that an individual initially consumes a substance for the ability of the agent to
produce a pleasurable effect (that is, reward) and that
dependence develops as a function of this recurrent drive
for reward (Wise, 1980). This idea of positive reinforcement
by drugs of abuse has been widely seen as a primary factor
behind drug dependence (Gill *et al*., 1988). However, many
drugs produce tolerance with repeated use, in that there is a
decrease in the reinforcing properties of the drug, leading to
compensatory increases in dosage that can exacerbate
neurophysiological alterations prototypical of addiction.
Some drugs, including psychostimulants, also produce an
opposing response of inverse tolerance, or sensitization, on
selected aspects of behaviour (Kalivas and Stewart, 1991;
Anagnostaras and Robinson, 1996). Although tolerance and
sensitization can concurrently exist and likely involve
different properties of the same neural circuits involved,
long-term drug use often results in aversive psychological
and physiological effects if intake is withheld, thus resulting
in continued use as a means to avoid the aversive
consequences of drug withdrawal (that is, negative reinfor-
cement) (Cami and Farre, 2003). Although both positive and
negative reinforcement theories provide some insight into
the initiation and maintenance of compulsive drug use,
respectively, these theories are unable to fully explain many
aspects of drug dependence, such as the resumption of drug-
seeking and drug-taking behaviours following a prolonged
period of abstinence (that is, relapse) when overt withdrawal
symptoms have long dissipated. Thus, although theories of
conditioning (both positive and negative reinforcement)
may account for some aspects of the persistence of drug
addiction (Wilker, 1973), none of these theories can fully explain
all aspects of the addiction cycle. Notably, more
recent theories have attempted to comprehensively explain
the complexities of addiction by hypothesizing that pro-
longed drug use results in a series of neuroadaptations,
which contribute to the enduring nature of the compulsive
addictive state.

In one theory, Koob and Le Moal (1997) have suggested
that continued exposure to the abused drug results in a
pathological shift of the drug user’s hedonic set point and
a state of dysregulation of brain reward systems that result in
a loss of control over drug intake and compulsive use. That
is, drug use produces disequilibrium in brain reward systems
for which the individual allostatic processes, or the ability to
achieve stability (or homeostasis) through change, cannot be
maintained. Enhanced sensitivity and counteradaptation of
the brain’s reward system are hypothesized to be at the
centre of this shift in hedonic homeostatic regulation, all
the while involving opposing alterations in mesolimbic
dopamine (DA), opioid and stressor hormone functions.
Alternatively, Robinson and Berridge (Robinson and Berridge,
1993; Berridge and Robinson, 1995) have put forward an
‘incentive sensitization’ theory of addiction, whereby they
postulate that abused drugs produce alterations in a number of
neural systems, particularly brain areas normally involved in
incentive motivation and reward for natural appetitive reinfor-
cers. Chronic drug use results in the addict becoming endur-
ingly hypersensitive to the drug and drug-associated stimuli (for
example, Clark and Overton, 1998), leading to a shift from drug
‘liking’ to drug ‘wanting’, with ensuing compulsive patterns of
drug-seeking behaviour.

More recently, several theories have centred on particular
aspects of drug-induced neuroadaptations that may specific-
ally explain the process and persistence of drug addiction.
Theories proposed to explain the persistent nature of
addictive behaviours include the formation of ingrained
drug habits in the form of aberrant stimulus response
learning (Wise, 2002; Everitt and Robbins, 2005; Volkow
*et al*., 2006), alterations in prefrontal cortical activity leading to
reductions in behavioural control and decision-making
skills (Jentsch and Taylor, 1999; Franklin *et al*., 2002;
Goldstein and Volkow, 2002) and overlaps between limbic
and cortical areas involved in addiction and memory
(Hyman and Malenka, 2001) that results in maladaptive
associative learning (Di Chiara, 1999). Each of these theories
contributes unique perspectives and testable hypotheses for
addiction research, and there is often considerable overlap
among these different perspectives. However, none of these
theories can fully account for all aspects of addiction, given
the multilayered complexity of addiction states and their
prevalency, which must account for biological, sociological,
economic, legal and cultural factors. Although advances in
neurobiological approaches in humans, notably modern
neuroimaging techniques, have allowed researchers to more
clearly delineate neural substrates that underlie addiction,
we will focus particularly on the utility of animal models in
this current review and special journal issue as a means to
provide novel insights into the biological basis of addictive
behaviours.

**Animal models of addiction**

Whereas clinical research in human addicts has elucidated
the extent, demographics and cycle of substance abuse
disorders, a variety of increasingly sophisticated animal
models have provided an invaluable means for under-
standing the neurobiology of addiction and the neuro-
pharmacological action of drugs of abuse. Examples of such
models include intracranial self-stimulation (ICSS), condi-
tioned place preference (CPP), behavioural sensitization and
self-administration paradigms (Balster, 1991). In the ICSS
model, animals previously implanted with intracranial
electrodes into certain brain areas (commonly involving the
medial forebrain bundle) will respond to receive a short
train of electrical stimulation (Gallistel, 1983). In light of the
hypothesis that ICSS involves brain areas that are involved in
motivation and reward, drugs of abuse have been found to
decrease ICSS thresholds (that is, because of their reinforcing
properties, addictive drugs reduce the amount of brain
stimulation sought by the subject). Moreover, research
indicates that the more addictive a substance, the greater
its ability to reduce ICSS thresholds (Kornetsky *et al*., 1979;
Kornetsky and Bain, 1990), suggesting that this model may
provide a means for evaluating an agent’s abuse potential.
ICSS has also served as a unique experimental tool to assess
changes, or dysregulation, in the basal hedonic state of an
animal following chronic drug exposure, in that withdrawal
from all major drugs of abuse has been shown to produce
contrasting increases in ICSS thresholds (Markou and Koob,
In the CPP model, animals are exposed to an apparatus generally consisting of two initially neutral environments that can differ in terms of a number of stimulus modalities, including colour, texture, odour and lighting (for reviews, see Carr et al., 1989; Tzschentke, 1998; Bardo and Bevins, 2000). Animals are exposed to one environment following drug pretreatment, whereas the other environment is paired with vehicle pretreatment. After a number of conditioning sessions, the animals (in a drug-free state) are allowed free access to the apparatus and the preference for one of the two environments is assessed. According to the principles of classical conditioning, if a drug has reinforcing properties, then the animal should prefer the previously drug-paired environment. Consistent with this hypothesis, various drugs of abuse, including opiates, nicotine and cocaine, typically induce CPP (Swerdlov et al., 1989). The CPP procedure has proven to be a useful and inexpensive means for assessing rewarding properties in a fairly quick manner, in that animals require no surgery and minimal training (Bardo and Bevins, 2000). CPP is also advantageous in that it can sometimes be established using a single drug pairing, is sensitive to relatively low drug doses and the animal can be tested in a drug-free state (Carr et al., 1989). However, the CPP model also possesses a number of limitations, including the methods of drug administration (intraperitoneal or subcutaneous injections), a potential confound of novelty on the test day, difficulties in generating data for dose–effect curves and it has generally only been demonstrated in rodents.

The behavioural sensitization model involves a progressive increase in the motor stimulatory effects of a drug following repeated intermittent administration. The development of behavioural sensitisation has been hypothesized to represent a shift from drug ‘liking’ to ‘wanting’ underlying compulsive drug use (Robinson and Berridge, 1993). This phenomenon has been demonstrated for a variety of drugs of abuse (Masur and Boerngen, 1980; Bartoletti et al., 1983; Kolta et al., 1985) and may relate to drug craving and relapse associated with drug addiction (Kalivas et al., 1998; Vanderschuren and Kalivas, 2000). Although useful for several aspects of drug-induced neuroplasticity, the behavioural sensitization model, such as CPP, is fundamentally limited because animals never experience contingent drug administration, which is the hallmark of addiction.

Although ICSS, behavioural sensitization and CPP models have been useful for delineating various aspects of the behavioural pharmacology of abused drugs, such as providing a means for evaluating the neurobiology and neurochemical systems underlying the effects of chronic drugs of abuse, the most widely accepted animal model of addiction is the self-administration paradigm. In this model, animals are trained to perform an operant behaviour (for example, lever press or nose poke) to receive a drug reinforcer. Similar to humans, animals will readily self-administer most drugs of abuse (for reviews, see Schuster and Thompson, 1969; Spealman and Goldberg, 1978; Balster and Lukas, 1985; Young and Herling, 1986), including opiates (Weeks, 1962; Blakesley et al., 1972), cannabinoids (Takahashi and Singer, 1979; Justinova et al., 2003), alcohol (Wood et al., 1971; Anderson and Thompson, 1974), nicotine (Hanson et al., 1979; Ator and Griffiths, 1983), amphetamines (Pickens et al., 1967; Pickens and Harris, 1968; Balster et al., 1976) and cocaine (Pickens and Thompson, 1968; Goldberg and Kelleher, 1976), with studies almost universally demonstrating that animals will preferentially respond on a reinforced (that is, active), rather than a non-reinforced (that is, inactive) operandum. Although a variety of species and routes of drug administration can be used, most studies involve the use of rodents (Weeks, 1972; Smith and Davis, 1975) or non-human primates (Deneau et al., 1969; Stretch and Gerber, 1970) self-administering drugs orally (Anderson and Thompson, 1974; Yanura et al., 1980), intracranially (Bozarth and Wise, 1981; Phillips et al., 1981) or intravenously via a chronic indwelling catheter (Griffiths et al., 1978; Spealman and Goldberg, 1978). The abuse potential of a drug in humans can be predicted from animal intravenous self-administration models (Collins et al., 1984), which clearly models the clinical abuse of drugs far better than repeated experimenter-delivered drug via intraperitoneal or subcutaneous administration (Markou et al., 1993). Given that the self-administration model has demonstrated good face and construct validity, this approach has provided an excellent tool for examining the neuropharmacological and neuroanatomical bases of the acute reinforcing effects of drugs of abuse, as well as their effects throughout the addiction cycle that result in individuals becoming ‘addicted’ and susceptible to relapse, even following prolonged periods of withdrawal or abstinence.

**Drugs of abuse**

Drugs of abuse are generally classified into different categories, including narcotics (for example, opiates), cannabinoids (for example, marijuana), depressants (for example, ethanol), stimulants (for example, nicotine, amphetamines and cocaine), hallucinogens (for example, lysergic acid diethylamide and ecstasy) and inhalants (for example, toluene and nitrous oxide). Although these drugs have a common ability to both produce feelings of pleasure and relieve negative emotional states (Nesse and Berridge, 1997), abused drugs have highly diverse behavioural and neuropharmacological properties. For example, in addition to analgesic properties, opiates cause a reduction in anxiety and behavioural inhibition, decreased sensitivity to stimuli, euphoria and sedation (for example, drowsiness and muscle relaxation). Opiates act on a variety of opioid receptor subtypes, including mu (µ), kappa (κ) and delta (δ) receptors. However, it is predominantly their interaction with µ receptors, which are widely dispersed across a variety of brain regions, including the cortex, striatum, thalamus, hippocampus, locus coeruleus, in addition to the ventral tegmental area (VTA), nucleus accumbens (NAc) and amygdala via direct actions on interneurons, that appear to mediate their behavioural and reinforcing properties. For example, µ receptor-deficient mice fail to display CPP following pretreatment with heroin (Contarino et al., 2002), whereas central and systemic administration of opioid receptor antagonists have been shown to change the pattern of morphine (Goldberg et al., 1971; Weeks and Collins, 1976) or heroin (Koob et al., 1984; Vaccarino et al., 1985)
self-administration, an effect consistent with a reduction in its reinforcing properties.

Similar to opiates, both cannabinoids and ethanol produce feelings of euphoria, disinhibition, relaxation and analgesia, as well as impaired performance on cognitive and psychomotor tasks. Δ²-tetrahydrocannabinol, the active ingredient in cannabis, primarily binds to the cannabinoid receptor CB₁. The CB₁ receptor is highly expressed in a number of brain regions, including the cortex, hippocampus, striatum and cerebellum (Herkenham et al., 1991; Tsou et al., 1998). These receptors are also found in the VTA, NAcc and amygdala via interneurons, and are hypothesized to mediate many of the central properties of cannabinoids, as indicated by an absence of many of its effects in CB₁-deficient mice (Ledent et al., 1999). Whereas Δ²-tetrahydrocannabinol has rather specific binding properties, the reinforcing effects of ethanol likely occur due to its interaction with a wide variety of neurotransmitter systems, including GABA (GABAₐ receptors in the VTA and NAcc), opioid peptides (Δ receptors), glutamate (NMDA receptors), ACh (nicotinic receptors) and serotonin (5-HT₃ receptors), with selective antagonists of these receptors reducing self-administration of ethanol in a number of studies (Altshuler et al., 1980; Fadda et al., 1991; Rassnick et al., 1993a).

Similar to other stimulants, nicotine produces an increase in arousal and energy (Benowitz, 1996), an enhancement in cognitive performance and learning (Wesnes et al., 1983; Levin et al., 1998) and a reduction in appetite. Although nicotine increases physiological arousal, smokers report a paradoxical reduction in stress and anxiety after smoking (Nesbitt, 1973), an effect likely contributing to the addictive profile of nicotine. Although an interaction with other neurotransmitter systems may also play a role (for example, glutamate, GABA and opioid peptides; Koob and Le Moal, 2006), nicotine’s reinforcing properties appear to be primarily mediated by its direct affinity for nicotinic ACh receptors in the VTA, NAcc and amygdala. Studies using various nicotinic receptor antagonists support this hypothesis in that these agents block nicotine self-administration in rats (Corrigall and Coen, 1989; Corrigall et al., 1994; Watkins et al., 1999), whereas local infusions of nicotinic receptor antagonists into the VTA have been shown to produce similar antagonist effects in self-administration (Corrigall et al., 1994) and ICSS studies (Panagis et al., 2000).

Psychomotor stimulants, such as amphetamines and cocaine, produce similar physiological and subjective effects in humans, including an increase in blood pressure, heart rate and respiration, increased stimulation and confidence, exhilaration, a reduction in fatigue and appetite, as well as increased performance on simple cognitive and motor tasks (Smith and Beecher, 1959; Fischman and Schuster, 1982; Wiegmann et al., 1996). In terms of their neurochemical actions, psychostimulants increase the synaptic availability of several monoamines, including serotonin (5-HT), DA and norepinephrine (NE), either indirectly by inhibiting their reuptake (for example, cocaine; Woolverton and Johnson, 1992) or directly by enhancing their release from presynaptic terminals (for example, amphetamines; Seiden et al., 1993; Kuczenski and Segal, 1994). However, the acute reinforcing effects of psychostimulants appear to be mediated primarily by increasing synaptic levels of DA in the NAcc via inactivation or reversal of DA transporters. In addition to more specific neurobiological evidence discussed in the next section, data supporting the role of DA in psychostimulant reward include a correlation between DA reuptake blockade and the reinforcing effects of cocaine (Ritz et al., 1987) or β-amphetamine (Ritz and Kuhar, 1989), as well as a positive relationship between DA transporter occupancy and the reported subjective effects of cocaine in humans (Volkow et al., 1997). However, some studies have questioned the primacy of enhanced DA levels as the main explanation for the reinforcing properties of psychostimulants, in that DA transporter knockout mice will readily self-administer cocaine (Rocha et al., 1998). Although initially interpreted as a strike against the DA hypothesis of reinforcement, it has subsequently been demonstrated that there is an increase in NAcc DA levels in DA transporter knockout mice exposed to cocaine or amphetamine. However, these effects are likely due to inactivation of NE (Carboni et al., 2001) and/or 5-HT (Mateo et al., 2004) transporters, thus supporting the major tenet that DA likely underlies psychostimulant reinforcement.

**Common neurobiology of addictive drug action**

Although drugs of abuse often produce differential behavioural effects and have diverse pharmacological profiles, one common feature they share is an enhancement in mesocorticolimbic DA activity (Wise, 1996), albeit their interaction with this system occurs at different levels (Cami and Farre, 2003). This circuit, which has been extensively implicated for its involvement in the rewarding properties of both natural stimuli (for example, food, drink and sex) and addictive drugs, consists of DA projections from cell bodies in the VTA to limbic structures (that is, mesolimbic pathway, such as the amygdala, ventral pallidum, hippocampus and NAcc) and cortical areas (that is, mesocortical pathway, including the prefrontal cortex (PFC), the orbitofrontal cortex (OFC) and the anterior cingulate). Interestingly, these corticostriatalimbic circuits operate in parallel, but may have somewhat different roles in addiction (Cami and Farre, 2003). For example, whereas the NAcc (Di Chiara, 2002) and ventral pallidum appear to be involved in the primary reinforcing effects of drugs of abuse (Volkow et al., 2003), the amygdala and hippocampus play an important role in conditioned learning engaged in the process of addiction. In the case of the amygdala (See, 2005) and ventral hippocampus (Rogers and See, 2007), this learning involves discrete stimulus-reward associations, whereas the dorsal hippocampus mediates stimulus-stimulus associations that may be particularly important for contextual learning (Fuchs et al., 2005, 2007). On the other hand, the PFC, OFC and anterior cingulate regulate emotional responses, cognitive control and executive function (Volkow et al., 1993), with repeated drug exposure leading to cellular adaptations of the prefrontal–Nacc glutamatergic pathway that contribute to persistent addictive behaviours, including diminished cognitive control and hyper-responsiveness to drug-associated stimuli (Kalivas and Volkow, 2005).
Together, these results suggest that the mesolimbic pathway is involved in the acute reinforcing effects of drugs and various conditioned responses related to craving and relapse, whereas changes in the mesocortical pathway mediate the conscious drug experience, drug craving and a loss of behavioural inhibition related to compulsive drug-seeking and drug-taking behaviours.

In general, all addictive drugs produce an enhancement in extracellular DA levels in the NAcc. DA release appears necessary for reward (Di Chiara and Imperato, 1988; Koob and Bloom, 1988), an effect hypothesized to provide positive reinforcement for drug self-administration and, as such, the initiation of the addiction cycle. Although natural reinforcers also produce an increase in DA release, the effect is not nearly as robust, and unlike addictive drugs, undergoes habituation (Di Chiara, 1999). These differences suggest that drugs of abuse not only ‘hijack’ a system normally implicated in the rewarding and reinforcing effects of stimuli involved in survival functions (Robbins and Everitt, 1996) but also the effect is persistent, adding to the consolidation of responses to drug-associated stimuli (Berke and Hyman, 2000) and further promoting the repeated use of the addictive substance.

Evidence implicating the mesolimbic DA system in the reinforcing effects of drugs of abuse includes findings that lesions of the NAcc, VTA and ventral pallidum severely attenuate cocaine and heroin self-administration (Roberts et al., 1980; Roberts and Koob, 1982; Hubner and Koob, 1990). Furthermore, extracellular DA levels are reliably increased in the NAcc during cocaine self-administration (Weiss et al., 1992; Meil et al., 1995; Wise et al., 1995b), whereas systemic administration of DA synthesis inhibitors (for example, Pickens et al., 1968; Wilson and Schuster, 1974) and DA antagonists (for example, Yokel and Wise, 1975; Woolverton, 1986; Rassnick et al., 1992; Richardson et al., 1994) have been shown to decrease the self-administration of a variety of drugs in animals, including cocaine, amphetamines, opiates and ethanol. More specific manipulations of the mesocorticolumbic system have demonstrated a similar effect for some drugs, in that kainic acid lesions of cell bodies in the NAcc block cocaine, heroin (Zito et al., 1985) and morphine self-administration (Dworkin et al., 1988b). Although DA receptor antagonist infusions or selective lesions of DA neurons in the NAcc using 6-hydroxydopamine (6-OHDA) can block psychostimulant self-administration (Roberts et al., 1977; Lyness et al., 1979), these manipulations generally fail to affect the self-administration of ethanol (Rassnick et al., 1993b) or opiates (Ettenberg et al., 1982; Pettit et al., 1984; Dworkin et al., 1988a), suggesting DA-independent mechanisms of reinforcement. In support of this hypothesis, intracranial or systemic administration of various opiate receptor antagonists has been found to attenuate heroin (Bozarth and Wise, 1983; Corrigall and Vaccarino, 1988) or ethanol (Altshuler et al., 1980; Samson and Doyle, 1985) self-administration. The endogenous cannabinoid system may also play a role in opiate and ethanol reward, in that genetic deletion (Ledent et al., 1999; Hungund et al., 2003) or antagonism of CB1 receptors (Caille and Parsons, 2003; Colombo et al., 2005) results in reduced ethanol or opiate intake. However, some evidence supports the notion that ethanol and opiates produce reinforcement by mesolimbic DA release (Johnson and North, 1992; Weiss et al., 1993), suggesting that their reinforcing properties likely involve both DA-dependent and -independent mechanisms (Van Ree et al., 1999).

In support of the hypothesized role of DA in opiate and ethanol reinforcement, in vivo microdialysis studies have demonstrated an increase in extracellular DA in the shell of the NAcc in animals during active self-administration of morphine (Pontieri et al., 1995), heroin (Hemby et al., 1995; Wise et al., 1995a) and ethanol (Weiss et al., 1993; Melendez et al., 2002; van Erp and Miczek, 2007). Similar effects have been reported during active self-administration for a variety of other drugs of abuse, including cannabinoids (Fadda et al., 2006; Lecca et al., 2006a), nicotine (Pontieri et al., 1996; Lecca et al., 2006b), amphetamines (Di Ciano et al., 1995; Pontieri et al., 1995) and cocaine (Hurd et al., 1989; Pettit and Justice, 1989; Di Ciano et al., 1995; Pontieri et al., 1995).

Interestingly, some studies (for example, ethanol; Melendez et al., 2002; van Erp and Miczek, 2007) have reported an increase in DA immediately prior to the initiation of the self-administration session, indicating that conditioned increases in NAcc DA occur when animals ‘anticipate’ drug consumption. Similar effects have been demonstrated when animals are exposed to reward-associated cues (Tobler et al., 2003; Cheer et al., 2007), suggesting that sensitization of mesoaccumbens DA release may result in the enhancement of the motivational value of drug-associated stimuli (Schultz et al., 1997).

Finally, animals will consistently respond for intracranial microinjections of various drugs of abuse (Myers, 1974; Bozarth, 1987), further supporting the role of the mesocorticolumbic system in addiction. Although laboratory animals will reliably self-administer opioids, such as morphine and fentanyl, into a number of mesocorticolumbic brain areas, including the VTA (Van Ree and de Wied, 1980; Bozarth and Wise, 1981, 1982) and NAcc (Olds, 1982), this effect appears relatively selective as animals will not self-administer opiates into other brain regions. Similarly, both alcohol-prefering and Wistar rats have been shown to self-administer a variety of doses of ethanol into the VTA (Gatto et al., 1994; Rodd et al., 2004a, b), with both groups of rats reducing responding when artificial CSF was substituted for ethanol. Rats and monkeys will also self-administer microinjections of amphetamine into a number of brain nuclei integrated within the mesocorticolumbic system, such as the OFC (Phillips et al., 1981), amygdala (Chevrette et al., 2002) and NAcc (Monaco et al., 1981; Chevrette et al., 2002). In one study (Hoebel et al., 1983), rats with NAcc cannulae responded preferentially on an active lever and demonstrated an alteration in lever preference when the response outcome was switched to the previously inactive lever. Moreover, responding was appropriately reduced when animals were pretreated with amphetamine and demonstrated extinction-like responding when reinforcer delivery was switched to ventricular delivery. Rats self-administering cocaine demonstrate a similar pattern of neuroanatomical specificity, in that they will respond for microinusions of cocaine into the shell, but not the core, of the NAcc (Rodd-Henricks et al., 2002), whereas other studies have demonstrated similar drug

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Neurobiology of drug dependence and relapse

In contrast to initial increases in neurotransmitter activity following acute drug exposure (for example, DA and glutamate) (Ungless et al., 2001; Vorel et al., 2002), research indicates that chronic administration leads to more complex changes in activity in the NAcc, especially during prolonged withdrawal. Some examples include alterations in GABA neurotransmission during alcohol withdrawal (Dahchour and De Witte, 2000), downregulation of nicotinic receptors during nicotine withdrawal (Mugnaini et al., 2006) and a reduction in DA neurotransmission (Weiss et al., 1992; Chefer and Shippenberg, 2002), and opposing opioid receptor responses (Koob et al., 1992) in the NAcc throughout psychostimulant and opioid withdrawal, respectively. Similarly, all drugs of abuse have been shown to produce dysregulations in brain stress systems (for example, alterations in adrenocorticotrophic hormone, corticosterone and corticotropin-releasing factor (CRF) activity) (for reviews, see Kreek and Koob, 1998; Koob, 1999; Koob and Kreek, 2007). These persistent alterations in stress hormone systems, receptor and/or neurotransmitter activity may represent compensatory mechanisms involving neuroadaptations aimed at restoring homeostatic function in response to the presence of the drug. As such, these changes could contribute significantly to negative emotional states characteristic of acute drug withdrawal, as well as enhanced sensitivity to stressful stimuli, both of which could result in greater vulnerability to relapse during abstinence in humans (Koob and Le Moal, 1997; Weiss et al., 2001).

As previously mentioned, relapse to drug-seeking and drug-taking behaviours following prolonged periods of abstinence constitutes one of the most significant problems for the long-term treatment of drug-dependent individuals (Dackis and O’Brien, 2001; Wagner and Anthony, 2002). A number of factors are known to contribute to craving and relapse, including exposure to environmental stimuli previously paired with drug use (that is, conditioned drug cues), negative mood states or stress. For example, abstinent cocaine users report greater drug craving following exposure to cocaine-associated stimuli (Childress et al., 1993), in response to non-contingent cocaine doses (Jaffe et al., 1989), and following stressful life events (Sinha et al., 1999). These trigger factors have been used in animal models of relapse to drug-seeking behaviour, particularly in the extinction–reinstatement model following withdrawal from chronic drug self-administration (See, 2002; Shaham et al., 2003). Typically, animals are trained to self-administer a drug (for example, cocaine) for prolonged periods of time. After chronic self-administration, animals experience extinction training, whereby responding on the previous drug-paired lever does not result in primary reinforcement. Extinction allows for a low baseline against which operant responding can be compared when the subjects are re-exposed to previously drug-paired cues (these may be discrete conditioned stimuli or contextual stimuli), non-contingent drug administration or exposure to environmental stressors (for example, footshock). Conditioned cues, drug priming and stress have all been shown to robustly reinstate drug-seeking behaviour (that is, induce relapse) as indexed by an increase in responding on a previously drug-paired operandum (Shaham et al., 2003). The development and application of the reinstatement model have been very useful for extensive exploration of the neural circuitry underlying relapse (Meil and See, 1997; Neisewander et al., 2000; Weiss et al., 2000; Kruzich and See, 2001).

Using the reinstatement model of relapse, a number of laboratories have contributed to mapping the neurocircuitry necessary to maintain relapse-like behaviour. In studies that have examined cue-induced drug-seeking behaviour, a significant amount of evidence has shown an important role for the dorsomedial PFC (dmPFC) and amygdala (particularly an area comprised of the lateral and basal nuclei or basolateral amygdala (BLA)), via glutamatergic and D2ergic interactions with the NAcc core. For example, exposure to explicit heroin-associated cues (Koya et al., 2006) or discriminative stimuli predicting cocaine (Ciccioppo et al., 2001) or ethanol availability (Dayas et al., 2007) results in concurrent increases in drug-seeking behaviour and Fos expression in the dmPFC, an effect that can be blocked by D1 receptor antagonism (Ciccioppo et al., 2001). Moreover, reversible inactivation of the dmPFC using the sodium channel blockers tetrodotoxin (McLaughlin and See, 2003) or lidocaine (Di Pietro et al., 2006), or the GABA_A and GABA_B agonists, muscimol and bacoferon (Rogers et al., 2008) has been shown to inhibit the reinstatement of drug seeking when rats are exposed to explicit cocaine- or heroin-associated cues. Similar inactivation of the lateral, but not medial, OFC has been shown to produce a comparable effect on the reinstatement of cocaine-seeking behaviour (Fuchs et al., 2004b).

Consistent with brain imaging studies indicating an increase in metabolic activity in the amygdala when abstinent cocaine users are presented with drug-associated cues or drug-related imagery (Grant et al., 1996; Childress et al., 1999; Kilts et al., 2001, 2004; Bonson et al., 2002), permanent lesions or reversible inactivation of the BLA have been shown to decrease responding for stimuli associated with cocaine reinforcement (Whitelaw et al., 1996; Meil and See, 1997; Grimm et al., 2000), as well as prevent the acquisition (Kruzich and See, 2001), consolidation (Fuchs et al., 2006b) and expression (Kruzich and See, 2001; Fuchs and See, 2002; McLaughlin and See, 2003; Rogers et al., 2008) of cocaine- or heroin-conditioned-cued reinstatement, suggesting that the BLA is critical for both the formation of
stimulus–drug associations and expression of conditioned-cued drug-seeking behaviour during relapse. In support of a major role of ascending DA inputs from the VTA, presentation of conditioned stimuli associated with cocaine availability significantly elevates extracellular levels of DA in the BLA (Weiss et al., 2000), whereas infusions of d-amphetamine into the BLA produces a significant enhancement of responding in the presence of drug-paired cues, with similar treatment failing to affect responding during extinction training (Ledford et al., 2003). Conversely, DA receptor antagonism in the BLA has been found to attenuate both the acquisition (Berglind et al., 2006) and expression (See et al., 2001) of conditioned-cued reinstatement, as well as cocaine-seeking behaviour using a second-order schedule of reinforcement (Di Ciano and Everitt, 2004b). Increases in amygdalar levels of Fos (Neisewander et al., 2000; Ciccolioppo et al., 2001) or Fos-related antigen (Franklin and Druhan, 2000) expression when animals are exposed to a cocaine-paired environment or cocaine-associated cues can also be reversed by DA D₁ receptor antagonism (Ciccionioppo et al., 2001). In addition to DA, cholinergic inputs to the BLA are critical for the acquisition, but not expression, of conditioned-cued reinstatement of cocaine seeking (See et al., 2003). Although the NMDA receptor antagonist d-2-amino-5-phosphonovalerate (D-APV) has been shown to attenuate the acquisition and consolidation of drug-paired stimulus learning (Feltenstein and See, 2007), intra-BLA infusions of NMDA and kainite/AMPA antagonists do not have any significant effect on the expression of conditioned-cued reinstatement (See et al., 2001). Overall, these results show that different afferent systems can regulate temporally unique aspects of amygdalar processing of drug-paired stimuli.

Similar to the BLA, a considerable amount of evidence has shown that the NAcc plays a key role in cue-induced reinstatement of drug seeking. For example, reversible inactivation of the NAcc core has been shown to selectively decrease cocaine seeking in both conditioned-cued reinstatement and second-order schedule of reinforcement models (Di Ciano and Everitt, 2004a; Fuchs et al., 2004a; Di Ciano et al., 2008). Exposing rats to an ethanol-associated discriminative stimulus resulted in the reinstatement of extinguished ethanol seeking, as well as an increase in Fos expression in the NAcc (Dayas et al., 2007). Moreover, microdialysis studies have indicated that exposure to discriminative stimuli predictive of cocaine availability causes an increase in DA in the NAcc (Weiss et al., 2000). More recently, Bossert et al. (2007) demonstrated an interesting dissociation between the role of DA D₁ receptors in the NAcc core and shell in respectively mediating drug-seeking behaviour following exposure to discrete cue or contextual stimuli associated with previous heroin reinforcement. Other neurotransmitter systems in the NAcc, including ACH and glutamate, also play important roles in drug-seeking behaviour. In one study, synaptic enhancement of NAcc ACh levels via systemic or microinjections of physostigmine (an acetylcholinesterase inhibitor) was found to inhibit the reinstatement of heroin seeking by conditioned cues (Zhou et al., 2007). In contrast to this effect, AMPA administration alone resulted in the reinstatement of extinguished cocaine-seeking behaviour (Cornish et al., 1999), whereas AMPA/kainate and/or NMDA receptor antagonism has been shown to block cocaine-seeking behaviour following exposure to drug-associated cues in a second-order schedule (Di Ciano and Everitt, 2001; Backstrom and Hyytia, 2007). Overall, these results collectively suggest that the reinstatement of drug-seeking behaviour following exposure to discrete or contextual drug-associated cues involves DAergic and glutamatergic interactions between the NAcc core and the BLA and dmPFC.

Similar to conditioned-cued reinstatement, a considerable amount of research suggests that the dmPFC and the NAcc core, as well as the VTA, mediate relapse behaviour following non-contingent exposure to the previously self-administered drug (McFarland and Kalivas, 2001). Inactivation of any of these three regions, in addition to the ventral pallidum, was found to dose-dependently attenuate cocaine-primed (Grimm and See, 2000; McFarland and Kalivas, 2001; Capriles et al., 2003) and heroin-primed (Rogers et al., 2008) reinstatement. Moreover, direct infusions of cocaine or DA into the dmPFC have been shown to reinstate cocaine seeking (McFarland and Kalivas, 2001; Park et al., 2002), whereas D₁/D₂ receptor antagonists in the dmPFC have the opposite effect (McFarland and Kalivas, 2001, but see Capriles et al., 2003). Although DA receptor antagonism was ineffective in the NAcc core (McFarland and Kalivas, 2001), infusions of the selective DA D₁ antagonist SCH-23390 into the shell of the NAcc did attenuate cocaine-primed reinstatement (Anderson et al., 2003), suggesting that DA in both subregions of the NAcc can regulate cocaine-primed reinstatement.

Further support for accumbal regulation of cocaine-primed reinstatement comes from studies showing that direct infusions of DA or glutamate into the NAcc can induce reinstatement of extinguished cocaine-seeking behaviour (Cornish et al., 1999; McFarland and Kalivas, 2001), an effect consistent with the observation that increases in DA, as well as glutamate, occur in the NAcc when animals are given a priming injection of cocaine (McFarland et al., 2003). More specific manipulations of glutamatergic function have shown that AMPA/kainic acid, but not NMDA, receptor antagonists can block cocaine-primed reinstatement when infused into the NAcc core (Cornish and Kalivas, 2000), whereas AMPA receptor agonists alone can elicit reinstatement responding (Cornish et al., 1999). Thus, although glutamate (via AMPA receptors) appears to play a more pivotal role in the NAcc core, it appears that DA in the shell of the NAcc may also functionally mediate cocaine-primed reinstatement.

As previously described, stress plays an important role in the vulnerability and motivation to abuse addictive substances (Higgins and Marlatt, 1975; Russell and Mehrabian, 1975; Koob and Le Moal, 2001). In animal models of relapse, reinstatement of drug seeking has been demonstrated using various stressors, including acute footshock exposure (Erb et al., 1996; Piazza and Le Moal, 1998; McFarland et al., 2004) and pretreatment with the NE α₂ receptor antagonist, yohimbine (Lee et al., 2004; Shepard et al., 2004; Le et al., 2005; Feltenstein and See, 2006), a drug that produces anxiety-like states in both humans (Holmberg and Gershon,
1961; Charney et al., 1983) and animals (Lang and Gershon, 1963; Davis et al., 1979), and increases drug craving in abstinent drug-dependent subjects (Stine et al., 2002). Examination of the neurocircuitry involved in stress-induced reinstatement has produced data suggesting that there is some overlap, as well as distinct differences, in these circuits relative to neural regulation of other types of reinstatement behaviour (Stewart, 2000; Shaham et al., 2003). Similar to cue- and drug-primed reinstatement studies, reversible inactivation of the dmPFC, NAcc or VTA has been shown to attenuate footshock stress-induced reinstatement of cocaine seeking, with data suggesting a unique role for the central nucleus of the amygdala (CeA) and the lateral bed nucleus of the stria terminalis (BNST) in mediating this behaviour (Capriles et al., 2003; McFarland et al., 2004). In studies examining specific neurotransmitter systems, CRF and NE, likely via interactions between the BNST and CeA, appear to be critically and selectively involved in stress-induced reinstatement. For example, systemic and intra-BNST and/or CeA administration of CRF (Shaham et al., 1997; Erb et al., 1998; Erb and Stewart, 1999; Le et al., 2000), or reduced NE activity via agonist activation of presynaptic zα-adrenoceptors or blockade of postsynaptic β-adrenoceptors (Erb et al., 2000; Shaham et al., 2000; Highfield et al., 2001; Leri et al., 2002), have been shown to attenuate footshock induced-reinstatement of drug seeking. Interestingly, and in contrast to cue- and drug-primed reinstatement, DA appears to play only a modulatory role in stress-induced reinstatement (Shaham and Stewart, 1996). However, based on evidence that DA D2 antagonist infusions into the dmPFC or OFC have been shown to block footshock-induced reinstatement of cocaine-seeking behaviour (Capriles et al., 2003), further study is warranted to explore the regionally selective role of DA in mediating these behaviours. Overall, results to date suggest that CRF and NE interactions within the CeA and BNST, as well as interactions of this pathway with the dmPFC and NAcc, may be critically involved in increased drug craving and a return to drug-seeking behaviour when addicts are exposed to stressful stimuli.

In summary, it appears that three distinct, yet overlapping, neurocircuits are involved in cue-, drug- and stress-induced reinstatement of drug-seeking behaviour (Kalivas and McFarland, 2003; Shaham et al., 2003). A series of projections, primarily involving DA and glutamate, from the VTA, BLA, dmPFC and NAcc core, appear to be the primary pathway mediating conditioned-cued reinstatement. Drug-primed reinstatement likely involves dmPFC glutamatergic projections to the NAcc core and DA innervations of the dmPFC and NAcc shell. Finally, stress-induced reinstatement involves noradrenergic and CRF inputs to the CeA and BNST that serially project to the dmPFC and NAcc core. Thus, although distinct in a number of aspects, this suggests that projections from the VTA (all forms of reinstatement), limbic regions of the BLA (cue reinstatement), CeA, BNST and NAcc shell (stress reinstatement) converge on motor pathways involving the dmPFC and NAcc core that represents a ‘final common pathway’ for all three types of instigating factors in relapse. It is important to note that additional research has demonstrated that other brain structures can play critical roles in driving drug-seeking behaviour, and that this is often dependent upon the nature of the withdrawal history or contextual environment that triggers relapse. For example, recent studies in humans (Volkow et al., 2006; Wong et al., 2006) have shown that increases in craving for cocaine are correlated with increases in DA in the dorsal striatum (caudate-putamen). In a similar manner, pharmacological blockade of the dorsolateral striatum can attenuate drug-seeking behavior in rats after forced abstinence (Fuchs et al., 2006a; See et al., 2007) or on a second-order schedule of reinforcement (Vanderschuren et al., 2005). Moreover, it has recently been demonstrated that the dorsal hippocampus (Fuchs et al., 2005) and NAcc shell, but not NAcc core (Bosser et al., 2007), play a significant role in contextual reinstatement of drug-seeking behaviour. Finally, the neuropeptide orexin (also known as hypocretin), which is predominately located in neurons in the lateral hypothalamus, has recently been found to play a significant role in mediating drug addiction and relapse (Harris et al., 2005), including the reinstatement of cocaine (Boutilier et al., 2005) and alcohol (Lawrence et al., 2006) -seeking behaviour following exposure to an acute stressor or drug-associated cues.

Conclusions

As a chronic disease (Meyer, 1996), drug addiction involves a number of personal, social and medical difficulties that usually persist for months or years after detoxification. Given the large social and economic impact of this disease, a considerable amount of research has sought to elucidate the role that behavioural and neuropharmaco logical factors may contribute to the transition from acute drug use to drug dependence, loss of control over use and compulsive drug-seeking behaviours that characterize addiction. From a neurobiological perspective, animal models have provided an invaluable means for determining the fundamental neurobiology involved in drug-seeking and drug-taking behaviours across the entire addiction cycle, including the acute reinforcing effects of drugs, neuroadaptational changes that occur during the transition to drug dependence and the relatively permanent alterations in these systems that underlie relapse. In general, research suggests that the mesocorticolimbic pathway, including the VTA, NAcc, amygdala and PFC via DA and glutamatergic pathways, plays a significant role in addiction. Notably, variations in neurotransmitter and/or neural systems have been seen across various classes of abused drugs and across different phases of the addiction cycle (for example, drug-taking versus drug-seeking behaviours). Although the current review has highlighted a number of findings on the general neural circuitry of addiction and relapse, latter sections in this issue will provide more comprehensive examinations of selective topics, including molecular, behavioural and neurobiological factors in addiction, the role and interaction of genes and the environment in addictive behaviours, and specific drugs of abuse. With a better understanding of the neurobiological factors that underlie drug addiction, continued preclinical and clinical research should aid in the
development of novel therapeutic interventions that may result in effective long-term treatment strategies for drug-dependent individuals.

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Conflict of interest
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